Carboplatin & Weekly Paclitaxel / EC (Epirubicin & Cyclophosphamide) with Pembrolizumab (Breast)

Indication

Neoadjuvant treatment of invasive triple negative breast cancer - ≥T2 N0 or any node positive

NB. Pembrolizumab is currently available via an MSD Patient Access Program for this indication, ensure local arrangements are in place before prescribing.

ICD-10 codes

C50

Regimen details

Cycles 1-4

Day	Drug	Dose	Route
1	Pembrolizumab	200mg	IV infusion
1	Carboplatin	AUC5*	IV infusion
1, 8, 15	Paclitaxel	80mg/m^2	IV infusion

* Carboplatin dose calculated using the Calvert equation: **Carboplatin dose (mg) = AUC (CrCl +25)**
Measured GFR (such as 24-hour urine or 51Cr-EDTA) is preferred whenever feasible, particularly in circumstances of co-morbidity that could affect renal function such as dehydration or extremes of weight. Alternatively, the Cockcroft and Gault method can also be used to estimate a patient's CrCl.
CrCl should be capped at 125mL/min.

Cycles 5-8

Day	Drug	Dose	Route
1	Pembrolizumab	200mg	IV infusion
1	Epirubicin	90mg/m^2	IV infusion
1	Cyclophosphamide	600mg/m^2	IV infusion

Cycle 9 onwards (adjuvant treatment)

Day	Drug	Dose	Route
1	Pembrolizumab	200mg every 3 weeks Or 400mg every 6 weeks	IV infusion

Cycle frequency

Cycles 1-8: 21 days
Adjuvant Pembrolizumab (to start after surgery): 21 or 42 days as above

Number of cycles

Maximum of 8 cycles of Pembrolizumab and chemotherapy before surgery
Maximum of 9 cycles of pembrolizumab 200mg every 3 weeks or 5 cycles of pembrolizumab 400mg every 6 weeks following surgery

Administration

Pembrolizumab should be administered in 100mL sodium chloride 0.9% over 30 minutes.

Pembrolizumab should be administered via an infusion set with an in-line sterile, non-pyrogenic, low protein binding filter (pore size 0.2 – 5.0µm).

After the infusion the line should be flushed with 30mL sodium chloride 0.9%.

Patients should be monitored every 30 minutes during the infusion (blood pressure, pulse and temperature) and for infusion related reactions. For mild to moderate reactions, decrease the infusion rate and closely monitor. Premedication with paracetamol and chlorphenamine should be used for further doses. For severe infusion related reactions discontinue treatment. Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of paclitaxel or carboplatin. Facilities for the treatment of hypotension and bronchospasm **must** be available.

Paclitaxel should be administered first.

Paclitaxel is administered in a 250-500mL sodium chloride 0.9% non-PVC infusion bag with a 0.22 micron in-line filter over 1 hour.

Carboplatin should be administered in 500mL glucose 5% over 30-60 minutes.

Epirubicin and cyclophosphamide are administered by slow IV bolus into the arm of a fast running drip of sodium chloride 0.9%. Cyclophosphamide may also be given as an IV infusion in 250-500mL sodium chloride 0.9% over 30 minutes.

Pre-medication

30 minutes prior to each paclitaxel infusion:
Chlorphenamine 10mg IV slow bolus
Dexamethasone 8mg IV slow bolus

Emetogenicity

Pembrolizumab, carboplatin + paclitaxel weekly cycles: moderate - high emetic potential on day 1 and moderate emetic potential on days 8 and 15.
Pembrolizumab-EC cycles: moderate - high emetic potential
Pembrolizumab single agent cycles: low emetic potential

Additional supportive medication

Mouthwashes as per local policy
Proton-pump inhibitor if required
Loperamide if required.
Scalp cooling may be offered

Primary GCSF prophylaxis:
Pembrolizumab, Carboplatin + weekly paclitaxel cycles: on days 3-5, days 10-12 and days 17-19.
Pembrolizumab-EC cycles: on days 2-8

Extravasation

Pembrolizumab is neutral (Group 1)
Paclitaxel is a vesicant (Group 5)
Carboplatin is an irritant (Group 3)
Epirubicin is a vesicant (Group 5)
Cyclophosphamide is neutral (Group 1)

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U+E (including creatinine)	14 days
LFTs	14 days
Thyroid function	14 days
Glucose	14 days
Calcium	14 days
Cortisol	At consultant discretion

Investigations – pre subsequent Pembrolizumab, carboplatin & weekly paclitaxel cycles

Investigation	Validity period
FBC*	24 hours
U+E (including creatinine)	96 hours
LFTs	96 hours
Thyroid function	6 weekly
Glucose	7 days
Calcium	7 days
Cortisol	At consultant discretion

* Additional FBC within 24 hours of day 8 and 15 doses.

Investigations – pre subsequent Pembrolizumab-EC cycles

Investigation	Validity period
FBC	96 hours
U+E (including creatinine)	7 days
LFTs	7 days
Thyroid function	6 weekly
Glucose	7 days
Calcium	7 days
Cortisol	At consultant discretion

Investigations – pre subsequent Pembrolizumab single agent cycles

Investigation	Validity period
FBC	7 days
U+E (including creatinine)	7 days
LFTs	7 days
Thyroid function	6 weekly
Glucose	7 days
Calcium	7 days
Cortisol	At consultant discretion

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	**Limit**
Neutrophils	≥ 1.0 x 10^9/L
Platelets	≥ 100 x 10^9/L
Creatinine Clearance (CrCl)	> 30mL/min (and <10% change)
Bilirubin	≤ ULN
AST/ALT	≤ 2 x ULN
Alkaline Phosphatase	≤ 2.5 x ULN

Dose modifications

- ### Haematological toxicity

Carboplatin + weekly paclitaxel cycles:

Neutrophils (x 10^9/L)		**Platelets** (x 10^9/L)	**Carboplatin dose**	**Paclitaxel dose**
≥ 1.0	and	≥ 100	100%	100%
< 1.0	or	< 100	Delay 1 week (or until recovery) then reduce dose by 1 x AUC	Delay 1 week (or until recovery)*
< 1.0	and	< 100	Delay 1 week (or until recovery) then reduce by 1 x AUC	Delay 1 week (or until recovery) then reduce dose to 70mg/m2*

*Omit paclitaxel if occurring on **day 8 or 15**

In the case of febrile neutropenia (neutrophils < 0.5 × 10^9/L and fever > 38.5°C requiring IV antibiotics) reduce paclitaxel to 60mg/m^2 and carboplatin by 1 x AUC for all subsequent doses.

EC cycles:
If neutrophils <1.0 x 10^9/L and/or platelets <100 x 10^9/L delay 1 week or until recovery. If febrile neutropenia despite GCSF or neutrophils < 0.5 x 10^9/L for more than 1 week consider reducing doses to 80% for future cycles.

Pembrolizumab:
Discuss with the consultant if:
Neutrophils <1.0 x 10^9/L
Platelets <75 x 10^9/L

- ### Renal impairment

Pembrolizumab: The safety and efficacy of pembrolizumab has not been studied in patients with renal impairment. No specific dose adjustments are recommended in mild to moderate renal impairment.
Discuss with consultant if CrCl <30mL/min.
Also see toxicity section below re: management of nephritis

Paclitaxel: no dose modification is required

Carboplatin:

CrCl (mL/min)	**Carboplatin dose**
> 30	100%
20-30	EDTA then 100% dose
< 20	Omit

If CrCl falls by more than 10% from the previous cycle then consider a dose reduction.

Epirubicin: There is no data available on use in severe renal impairment. Consider dose reduction if CrCl <10mL/min (consultant decision).

Cyclophosphamide:

CrCl (mL/min)	**Cyclophosphamide dose**
> 20	100%
10-20	75%
< 10	50%

- **Hepatic impairment**

Pembrolizumab: The safety and efficacy of pembrolizumab has not been studied in patients with hepatic impairment. No specific dose adjustments are recommended in mild hepatic impairment. See below for management of hepatitis.

Paclitaxel: Paclitaxel is not recommended in severe hepatic impairment. If bilirubin < 1.5 x ULN and AST/ALT < 5 x ULN proceed with 100% dose. For more severe hepatic impairment, treatment may only proceed on consultant's decision, at a reduced dose with weekly monitoring of LFTs.

Carboplatin: Transient increases in liver enzymes have been seen in patients being treated with carboplatin although no dose reduction is usually required. If bilirubin ≥ 3 x ULN and/or transaminases ≥ 5 x ULN discuss with consultant.

Epirubicin:

Bilirubin (x ULN)		**AST/ALT** (x ULN)		**Alkaline phosphatase** (xULN)	**Epirubicin dose**
< 1.5	and	≤ 2.0	and	≤ 2.5	100%
1.5 - < 3	or	> 2.0 -3.5	or	> 2.5 - <5	50%
≥3 - 5	or	> 3.5	or	5-10	25%
> 5			or	> 10	Omit

Cyclophosphamide: not recommended if bilirubin > 1.5 x ULN or AST/ALT > 3 x ULN (consultant decision).

- **Other toxicities**

Carboplatin and weekly paclitaxel:

Toxicity	**Definition**	**Carboplatin dose**	**Weekly paclitaxel dose**
Fatigue	Grade 3	100%	1st occurrence – reduce to 70mg/m^2 for all subsequent doses or omit
Neuropathy	Grade 2	100%	1st occurrence – reduce to 70mg/m^2 for all subsequent doses or omit
	Grade ≥ 3		Discuss with consultant

Epirubicin-Cyclophosphamide:

For grade 3 or 4 mucositis/stomatitis – delay until resolved to ≤ grade 1 and reduce epirubicin to 80% dose.

Pembrolizumab:
Patients must be advised to seek specialist advice if they experience side effects as these can worsen rapidly. Immune reactions may occur during or after completion of treatment.

Toxicity	Definition	Action
Colitis	Grade 1	Continue and closely monitor
	Grade 2-3	Withhold until symptoms resolve to ≤ grade 1
	Grade 4 or recurrent grade 3	Permanently discontinue pembrolizumab
Pneumonitis	Grade 1	Continue and closely monitor
	Grade 2	Withhold until symptoms resolve to ≤ grade 1
	Grade 3-4 or recurrent grade 2	Permanently discontinue pembrolizumab
Nephritis	Grade 2 (creatinine 1.5-3 x ULN)	Withhold until symptoms resolve to ≤ grade 1
	Grade 3 (creatinine > 3 x ULN)	Permanently discontinue pembrolizumab
Endocrine	Symptomatic hypophysitis	Withhold until symptoms resolve to ≤ grade 1
	Type 1 diabetes with grade > 3 hyperglycaemia (glucose > 13.9 mmol/L) or ketoacidosis	Withhold until ≤ grade 2 May consider recommencing after corticosteroid taper or discontinue.
	Hyperthyroidism ≥ grade 3	Withhold until ≤ grade 2 May consider recommencing after corticosteroid taper or discontinue.
	Hypothyroidism	Continue and manage with replacement therapy
Hepatitis	AST/ALT 3-5 x ULN or Bilirubin > 1.5-3 x ULN	Withhold until resolves to ≤ grade 1
	AST/ALT > 5 x ULN or Bilirubin > 3 x ULN	Permanently discontinue pembrolizumab
	If liver metastasis with baseline AST/ALT 3-5 x ULN: - If AST/ALT increases ≥ 50% for ≥ 1 week	Permanently discontinue pembrolizumab
Infusion-related reactions	Grade 3-4	Permanently discontinue pembrolizumab
Skin reactions	Grade 3 or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold until resolves to ≤ grade 1
	Grade 4 or confirmed SJS or TEN	Permanently discontinue
Other immune-related adverse reactions	Grade 3 or 4 myocarditis Grade 3 or 4 encephalitis Grade 3 or 4 Guillain-Barre syndrome	Permanently discontinue

Pembrolizumab should be permanently discontinued if:
- Grade 4 toxicity (except for endocrinopathies that are controlled with replacement hormones)
- Corticosteroid dosing cannot be reduced to ≤10 mg prednisolone or equivalent per day within 12 weeks
- Treatment-related toxicity does not resolve to Grade 0-1 within 12 weeks after last dose
- Any event occurs a second time at Grade ≥ 3 severity

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression
Infertility
Teratogenicity
Hypersensitivity reactions
Pneumonitis
Hepatic impairment
Cardiotoxicity
Electrolyte disturbances
Arrhythmias
Colitis
Hepatitis
Nephritis
Endocrinopathies
Pancreatitis

- **Frequently occurring side effects**

Diarrhoea
Constipation
Fatigue
Nausea and vomiting
Myelosuppression
Stomatitis and mucositis
Arthralgia and myalgia
Alopecia
Peripheral Neuropathy
Anorexia
Rash
Hyperglycaemia
Hypocalcaemia
Hyperthyroidism, hypothyroidism

- **Other side effects**

Fluid retention
Red urine (for 24 hours post epirubicin)
Deranged liver function
Phlebitis
Skin toxicity
Nail changes
Taste disturbances
Bladder irritation

Significant drug interactions – for full details consult product literature/ reference texts

Warfarin/coumarin anticoagulants: increased or fluctuating anticoagulant effects. Avoid if possible, consider switching patient to a low molecular weight heparin or DOAC during treatment or if the patient continues taking an oral anticoagulant monitor the INR at least once a week and adjust dose accordingly.

Phenytoin: requires close monitoring if using concurrently.

Pembrolizumab:
Corticosteroids: use of systemic corticosteroids at baseline, before starting pembrolizumab, should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of pembrolizumab. However, systemic corticosteroids or other immunosuppressants can be used after starting pembrolizumab to treat immune-related adverse reactions.

Carboplatin:
Aminoglycoside antibiotics: increased risk of nephrotoxicity and ototoxicity
Clozapine: increased risk of agranulocytosis, avoid concomitant use
Diuretics: increased risk of nephrotoxicity and ototoxicity
Nephrotoxic drugs: increased nephrotoxicity; not recommended
Phenytoin: carboplatin reduces absorption and efficacy of phenytoin
Yellow fever vaccine: contraindicated

Paclitaxel:
Clozapine: increased risk of agranulocytosis.
Paclitaxel is a CYP 2C8/9 and CYP 3A4 substrate. Drug levels may be increased by inhibitors of these enzymes and decreased by inducers of these enzymes.

Cyclophosphamide:
Amiodarone: increased risk of pulmonary fibrosis – avoid if possible
Azathioprine: increased risk of hepatotoxicity
Clozapine: increased risk of agranulocytosis – avoid concomitant use
CYP2B6 and CYP3A4 inhibitors (Nevirapin, Ritonavir): co-administration may reduce the efficacy of cyclophosphamide
Digoxin tablets: reduced absorption – give as liquid form
Indapamide: prolonged leucopenia is possible - avoid
Itraconazole: may increase adverse effects of cyclophosphamide
Grapefruit juice: decreased or delayed activation of cyclophosphamide. Patients should be advised to avoid grapefruit juice for 48 hours before and on day of cyclophosphamide dose.

Additional comments

Women of childbearing potential should use effective contraception during treatment and for at least 4 months after the last dose of pembrolizumab.

Epirubicin has a lifetime maximum cumulative dose of 900mg/m^2

References

- Summary of Product Characteristics Epirubicin (Accord) accessed 4 August 2022 via www.medicines.org.uk
- Summary of Product Characteristics Cyclophosphamide (Sandoz) accessed 4 August 2022 via www.medicines.org.uk
- Summary of Product Characteristics Paclitaxel (Accord) accessed 4 August 2022 via www.medicines.org.uk
- Summary of Product Characteristics Carboplatin (Accord) accessed 4 August 2022 via www.medicines.org.uk
- Summary of Product Characteristics Pembrolizumab - Keytruda® (MSD) accessed 4 August 2022 via www.medicines.org.uk
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